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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/219,200	03/29/94	LINSLEY	P 30436.11US01

EXAMINER

18M1/1210

SARAH B. ADRIANO
MANDELL & ADRIANO
725 MAIN STREET
HALF MOON BAY CA 94019

GAMBEL, P

ART UNIT	PAPER NUMBER
1806	49

DATE MAILED: 12/10/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/16/97

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 79-96 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 79-96 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

DETAILED ACTION

1. Applicant's amendments, filed 9/16/97 (Paper No. 46), is acknowledged. Claims 79-81, 84-90 and 93-96 have been amended.

Claims 1-78 have been canceled previously.
Claims 79-96 are pending.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's arguments, filed 9/16/97 (Paper No. 46). The rejections of record can be found in the previous Office Action (Paper No. 44).

3. Applicant should amend the first line of the specification to update the status of priority documents. USSNs 07/547,980 and 07/722,101 are now abandoned.

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 9.

Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views). Photographs are not acceptable until a petition is granted.

5. Upon reconsideration of applicant's amended claims, filed 9/16/97 (Paper No. 46), the previous rejection under 35 U.S.C. § 112, first paragraph, written description (i.e. new matter) as it would apply to the instant claims has been withdrawn.

6. The specification is objected to and claims 79-96 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention for the reasons of record set forth in the last Office Action (Paper No. 44). There is insufficient objective evidence that accurately reflects the relative efficacy of the claimed therapeutic strategies to inhibit T cell proliferation or to prevent binding of CD28 receptor to B7 antigen, commensurate in scope with the therapeutic methods encompassed by the claimed methods by employing soluble B7 and soluble CD28.

Applicant's arguments, filed 9/16/97 (Paper No. 46), have been fully considered but are not found convincing. Applicant argues that rejections based on the enablement of B7 and CD28 immunoglobulin fusion proteins have been raised and withdrawn. Applicant cites MPEP at 706.04 to indicate that the rejection of previously allowed claims is to occur only under certain defined circumstances.

Contrary to applicant's assertion, an examiner is not prohibited from making a new grounds of rejection provided it is warranted during the prosecution of a patent application. Applicant has the options of appealing or petitioning the patent application.

In addition, applicant's arguments concerning the enablement and scope of the instant methods were considered in the last Office Action (Paper No. 44). Applicant arguments, filed 1/28/97 (Paper No. 42), stated that the invention is directed to the discovery that B7 will recognize CD28 and vice-versa and that this recognition produces the effects claimed and, in turn, applicant is entitled to other soluble fusion proteins. However, for the reasons set forth in the last Office Action (Paper No. 44) including applicant's own disclosure and the art; soluble B7 and CD28 fusion proteins have not met the limitations of the instant methods. Therefore, not only have immunoglobulin fusion proteins comprising B7 and CD28 have not met the claimed limitations but neither have the various soluble proteins other than said immunoglobulin fusion proteins. Issues such as tissue distribution, half-life, affinity and avidity obtained with various CD28-B7-specific reagents on altering in vivo immune responses should be interpreted in light of the type of reagent infused. Applicant's arguments were fully considered but are not found convincing with respect to soluble fusion proteins in the claimed methods.

It is noted that the current rejection under 112, first paragraph, has relied upon new art and addresses the same reliance upon the in vivo efficacy of the CD28-B7 inhibitor CTLA-4Ig as applicant did in Paper No. 38, but with the opposite conclusions.

In addition, no claims were allowed in the Office Action, mailed 9/13/96 (Paper No. 39). Also, it was noted in this Office Action (section 21) that contacting CD28 positive T cells with B7 induces proliferation, which contrasts with the claimed methods to inhibit T cell proliferation via B7.

It is noted that the previous examiner withdrew the 112, first paragraph rejection (Paper No. 39) in response to applicant's amendment, filed 6/20/96 (Paper No. 38). Applicant relied upon page 46, paragraph 3 of the instant specification which discloses that B7Ig blocked CD28-mediated adhesion less effectively than mAb 9.3 (anti-CD28). Here, page 46, paragraph 3 of the instant specification discloses that CD28Ig failed to inhibit CD28-mediated adhesion at concentrations of up to 950 nM.

Applicant also relied upon page 71, paragraphs 1-2 of the instant specification which discloses that monoclonal antibodies 9.3 (anti-CD28) and BB-1 (anti-B7) block T_h cell-induced Ig productions by B cells.

In contrast to applicant's reliance on these limited in vitro experimental observations wherein soluble B7 exhibited limited ability to inhibit CD28-mediated adhesion and soluble CD28Ig exhibited no ability to inhibit CD28-mediated adhesion; no objective evidence was relied upon to use soluble B7 or soluble CD28 to inhibit T cell proliferation, to inhibit binding of CD28 positive T cell to B7 positive B cells , to inhibit CD28 positive T cell response, to inhibit the binding of B7 positive B cells to CD28 positive T cells, commensurate in scope with the claimed methods, encompassing the inhibition of transplant rejection, GVHD, autoimmunity (e.g. IDDM, myasthenia gravis, rheumatoid arthritis and SLE on page 72 paragraph 1 of the instant specification), infectious disease and neoplasia (see Uses In Vitro and In Vivo on pages 23-29) for the reasons of record set forth in Paper No. 44.

Applicant also relied upon the successful use of CTLA4 in vivo to support the enablement of soluble B7Ig and CD28Ig. the instant claims. The current examiner has also relied upon the results associated with CTLA-4Ig to support the 112, first paragraph, rejection set forth in the last Office Action (Paper No. 44).

As indicated in the previous Office Action (Paper No. 44), the instant B7Ig and CD28IG do not have the affinity, avidity or half-life that would be necessary to achieve the claimed methods commensurate in scope with therapeutic methods. As indicated in the previous Office Action, the administration of CTLA-4 Ig can result in immunosuppression as observed in several model systems, however even in these systems the timing of CTLA-4 Ig administration relative to the antigenic exposure of the mechanism by which the foreign antigens were introduced into the host (e.g. timing, dose and site) had significant impact on the success of the intervention. Also, it was noted that Blazar et al. (J. Immunol., 1996) discloses that issues such as tissue distribution, half-life, affinity and avidity obtained with these various CD28-B7-specific reagents might prove to be highly important in achieving GVHD protection. However, any conclusion regarding the efficacy of CD28/B7 blockade on altering in vivo immune response should be interpreted in light of the type of reagent infused (Blazar see page 3257, column 2, paragraph 10).

In contrast to the role that the CD28-B7 inhibitor CTLA-4 Ig appears to have in vivo, there is insufficient objective evidence in the instant application that either B7Ig or CD28Ig fusion protein alone can inhibit T cell function or interactions in vivo and the objective evidence of record would indicate that neither would be predicted to inhibit in vivo function or interactions.

The current examiner has relied upon adequate explanations with supporting evidence to maintain the rejection of record under 112, first paragraph, based upon the Forman factors. After evidence or arguments are submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument. Applicant's arguments have not been found persuasive in the absence of objective evidence to the contrary.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inhibiting T cell function and interactions by administering or providing soluble B7 and CD28 fusion proteins.

Applicant's arguments are not found persuasive.

7. Upon reconsideration that applicant indicated that ATCC 68627 (B7Ig) and 68628 (CD28Ig) plasmids were deposited under the Budapest Treaty that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in Paper No. 11; the previous rejection under 112, first paragraph, to satisfy the deposit of biological materials has been withdrawn.

8. Claims 79-96 are rejected under 35 U.S.C. § 112, first and second paragraphs, for the reasons of record set forth in the last Office Action (Paper No. 44).

Applicant's arguments, filed 9/16/97 (Paper No. 46), have been fully considered but are not found convincing. Applicant argues that the specification discloses that the defining characteristic of B7, namely that it is the B cell ligand for CD28 (specification at page 43) and that B7 is the single art accepted term for this molecule as first described in Freeman et al., J. Immunol, 143: 2741-2722 (1989).

However, the interaction of CD28 on T cells occurs with the B7 family molecules including B7-1/CD80 and B7-2/CD86 (for example, see Yi qun et al. International Immunology, 1996, Introduction). Here it is noted that testing human B cells are B7-negative and upon activation, B7-2 appears more rapidly than B7-1. Also, human peripheral blood monocytes constitutively express B7-2, where B7-1 is only expressed on monocytes after activation with IFN-γ or GM-CSF. Peripheral blood dendritic cells are CD80-negative and only express CD86 weakly, but both molecules are rapidly induced during culture. Therefore, B7 represents a family of distinct molecules which expression differs between cell types and cell activation.

In contrast to applicant's assertions that applicant need not disclose every known B7 molecules or that it would not have been undue experimentation to determine other members of a class of B7 binding molecules; the instant specification did not provide direction or guidance as to a family of B7 molecules, but rather relied upon the B7 molecule disclosed by Freeman et al. (See page 11, paragraph 1 of the instant specification).

Again, the recitation of the certain amino acid sequences are ambiguous and confusing since it is unclear as to what is the base amino acid sequence being relied upon. Again, applicant has enabled only the B7 antigen disclosed in Freeman et al. and, in turn, only those sequences and extracellular domains derived from said B7 antigen. Again, applicant is required to amend the claimed limitation to include a SEQ ID NO. for the B7 antigen.

Applicant is reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims.

Applicant's arguments are not found persuasive.

9. Applicant's amended claims, filed 9/16/97 (Paper No. 46), have obviated the previous rejections under 35 U.S.C. § 112, second paragraph,

10. No claim is allowed .

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12. This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $375 for a small entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
December 3, 1997

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800